67. The soluble fusion protein of claim 1, wherein the C-terminus of the ~~V-β chain is~~ covalently linked to the N-terminus of a Cβ chain fragment.

68. A recombinant bacteriophage comprising the soluble fusion protein of claim 1.

REMARKS

Claims 1, 9 and 20 have been amended and new claims 60-68 have been added to more particularly define the invention. Support for the amendment and new claims can be found throughout the application including the drawings and claims as filed.

For example, support for the amendment to claim 1 can be found, e.g., on page 9, first full paragraph; pages 22-23, bridging paragraph; and page 23, first full paragraph. Support for the amendment to claim 9 can be found, e.g., on pages 15-16, bridging paragraph. The amendment of claim 20 is supported, e.g., by disclosure on page 17, first full paragraph. New claims 60-64 have been rewritten using language from claims 5, 10, 11, 12, 16 (respectively) now cancelled. Claim 17 has been rewritten as new claims 65 and 66. Support for new claim 68 can be found, e.g., on page 19, second full paragraph and in Examples 14-15. New claim 67 finds support throughout the application, e.g., see page 15, second paragraph.

The present amendments and new claims introduce no new matter.

Applicants submitted a supplemental IDS on July 27, 1998. Consideration of that IDS and receipt of the Examiner's copy of the PTO-1449 form is requested.

The Office Action states that the present application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for reasons stated on an attached Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/or Amino Acid Sequence Disclosures ("Notice"). Office Action at 2. However, the undersigned has not

received the Notice. On receipt of that Notice, the undersigned will remedy any deficiency in the sequence listing submitted with the present application.

Claims 1-18 stand rejected under 35 U.S.C. §112, second paragraph on grounds that the term "soluble" is unclear. Applicants respectfully disagree with the rejection.

The word "soluble" as it is used throughout the application has clear and unambiguous meaning to those of skill in this particular field. In particular, the term "soluble" when it is used to reference a fusion protein generally means that the protein does not require refolding. A more specific definition can be found in the specification where a soluble fusion protein is reported to have recognized properties, e.g., stable secretion in culture medium, stability in substantially physiological conditions, lack of hydrophobic amino acids such as those found in the TCR transmembrane region, and minimal inclusion body formation. See page 29, second paragraph.

Accordingly, it is believed that the term "soluble", particularly when read in light of Applicants' disclosure is clear and unambiguous. Reconsideration and withdrawal of the rejection are requested.

Claims 6, 11, 12, 16, 17 and 19 stand rejected as being unclear for reciting the term "protein tag". Applicants respectfully disagree with the rejection.

Applicants' use of the term "protein tag" is readily understandable by one of skill in this particular field. For example, the specification discloses that a protein tag can be used to facilitate purification or to introduce a desired protease cleavage site in a fusion protein. See pages, 4-5 bridging paragraph. Illustrative attachment between the protein tag and the fusion protein is discussed, e.g., on pages 15-16, bridging paragraph and page 15, first full paragraph. See also Example 1.

Specific examples of recognized protein tags are disclosed throughout the application, e.g., see page 27 in which the well-known protein tags 6XHIS, EE, Myc are disclosed.

Additionally, page 27 teaches other specific protein tags such as those known sequences with a cleavage site for enterokinase, Factor Xa, snake venom, or thrombin. Additional examples of protein tags can be found in the published PCT Application No. WO 96/13593 cited on page 27, first full paragraph.

Accordingly, it is believed that one of skill would understand the term "protein tag" as being clear and unambiguous. Reconsideration and withdrawal of the rejection are requested.

Claims 1-20 stand rejected under 35 U.S.C. §112, second paragraph on grounds that the term "single-chain T cell receptor" is unclear. Applicants respectfully disagree with the rejection as to claims 9-17 as those claims do not recite the term "single-chain T cell receptor".

The rejection as it applies to claims 1-8, and 18-20 is believed to be addressed by this submission. In particular, claim 1 recites a single-chain T cell receptor that includes an antigen binding pocket. It is believed that the term "single chain T cell receptor", especially when used to reference the pocket is clear and unambiguous. Reconsideration and withdrawal of the rejection are requested

Claim 5 stands rejected under 35 U.S.C. §112, second paragraph as being unclear as to its dependency on claim 2. The rejection is believed to be addressed by the present submission. In particular, Applicants have adopted the claim suggested by the Examiner as new claim 60. See Office Action at 3.

Claim 10 stands rejected under 35 U.S.C. §112, second paragraph as being unclear as to its dependency on claim 9. Claim 10 has been rewritten as new claim 61 along lines suggested by the Examiner. See Office Action at 4.

Claims 11-17 stand rejected under 35 U.S.C. §112, second paragraph as being unclear as to their dependency on claims 10, 9, 13, 14 and 15, respectively. The rejections are believed to

be addressed by the present submission. In particular, claims 11-17 have been rewritten as new claims 62, 63, 64, 65, and 66.

Claim 9 stands rejected under 35 U.S.C. §112, second paragraph as being unclear as to whether " the N-terminus of the VIII protein must be covalently linked to the C-terminus of the V-β chain." Office action at 5. The rejection is believed to be addressed by the present submission.

The typographical error in claim 9 has been corrected.

Claim 20 stands rejected under 35 U.S.C. 112, second paragraph as being unclear for reciting the word "humanized". The rejection is believed to be addressed by the present submission.

Claims 1-20 have been rejected under 35 U.S.C. §112, second paragraph as being unclear for reciting TCR V-α and V-β chains. The position has been taken that the claims should be changed to recite "region" instead of "chain" and to point out specific TCR amino acid residues in the chains. Applicants respectfully disagree with the rejection.

Applicants' use of the terms V-α "chain" and V-β "chain" is believed to be clear and unambiguous to one of skill in this field. In particular, use of "chain" to reference a TCR V-α or V-β segment is recognized and accepted usage in this field. Applicants position is fully supported by references cited throughout the Background section and especially on page 2, first full paragraph. See also Choi U.S. Patent No. 5,616,472 e.g., at col. 2, lines 15-30 in which TCR "chains" are specifically referenced. The Choi patent is of record in this case. Reconsideration and withdrawal of this ground of rejection are requested.

The position has been taken that Applicants must point out which amino acid residues of the TCR are encompassed by the claims. Office Action at 6. Applicants respectfully disagree with this rejection.

The terms "V-α chain" and "V-β chain" are routinely used in this particular field without reference to specific amino acid residues. See generally Applicants' discussion of these chains in the Background section of the application. Both V-α or V-β chains are well-known and are recognized to be of a certain size range. See Applicants' disclosure on page 17.

In particular, claim 1 encompasses a fusion protein with an antigen binding pocket formed by the V-α and a V-β chains. It would be readily appreciated by one of skill in the field what approximate size of V-α and V-β chain is needed to form that pocket. Additional specificity is not required to understand these terms particularly as used in light of Applicants' disclosure. Reconsideration and withdrawal of this ground of rejection are respectfully requested.

In view thereof, it is believed that the present rejections under 35 U.S.C. §112, second paragraph should be withdrawn.

Claims 1-19 have been rejection under 35 U.S.C. §103 as being unpatentable over Barbas U.S. Patent 5,759,817 and Onda (*Molecular Immunol.* 32: 1387, 1995) in view of Schodin et al. (*Mol. Immunol.* 33: 819, 1996); Novotny et al. (*PNAS* 88: 8646, 1991), WO 96/18105, Ward (*Scand. J. Immunol.* 34: 215, 1991) or Kappler et al. (*PNAS* 91: 8462, 1994). The rejection is respectfully traversed.

In formulating the rejection, the position has been taken that it would be obvious to substitute an scTCR for the TCR part of the bacteriophage fusion protein allegedly taught by the Examiner's combination of Barbas and Onda. Office Action at 10. Applicants respectfully disagree with this position.

There is nearly universal recognition that scTCRs are difficult to manipulate. For example, most prior purification schemes give insoluble molecules in low yields. Oftentimes, optimal practice of the prior schemes requires significant refolding to obtain workable fusion protein. Applicants have particularly pointed to these problems in the specification. See e.g., pages 2-3. As examples, the WO 96/18105 reference discusses substantial problems producing an scTCR (see e.g., pages 26-29 in which solubility and refolding problems are discussed). Additional problems making and using scTCRs can be found in the Novotny reference (see e.g., page 864 discussing refolding of an insoluble scTCR). Still further problems are reported in the Schodin reference (reporting preparation of insoluble scTCRs on pages 819-822).

Barbas and Onda, when taken individually or in combination with the other cited references, do not teach how to overcome the solubility and refolding problems known to plague scTCRs. Accordingly, it would not be expected that fusing another protein such as a bacteriophage coat protein to the scTCR would remedy these problems. On the contrary, one of skill in this field would expect that fusing the scTCR to more protein would further confound scTCR manipulations, e.g., by decreasing solubility and increasing need for refolding.

It was Applicants who discovered that fusing the scTCR to a bacteriophage coat protein quite surprisingly increased scTCR solubility and eliminated need for significant refolding. This inventive concept is not taught or implied by the Examiner's combination of cited references. Additional advantages of Applicants' discovery are discussed throughout the application, e.g., on pages 3-4, 29 and the Examples.

There have been limited attempts to increase scTCR solubility by fusing the molecule to thioredoxin or maltose binding protein carrier. See the Schodin and WO/ WO 96/18105 references, respectively. Although these references report some increase in scTCR solubility, the disclosed fusion protein-carrier molecules are reported to need refolding. In contrast, Applicants fusion proteins are suprisingly soluble and do not require significant refolding. These references taken alone or in combination with the other cited references simply do not teach,

imply or provide any motivation for overcoming the refolding problems as Applicants have done.

Accordingly, there is no basis for the position that it would be obvious to make the scTCR bacteriophage coat protein fusion as alleged in the rejection. In particular, there is not support for the position that the TCR portion of Barbas' moleculeis interchangeable with the scTCR. Reconsideration and withdrawal of the rejection are requested.

The §103 rejection is traversed on several other grounds.

For example, the rejection states that Onda discloses making a single-chain T-cell receptor.

> Onda et al. disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a **single-chain T cell receptor** by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII.
>
> Office Action at 7 (emphasis added).

Applicants respectfully disagree with this reading of Onda. The reference does not disclose fusion of a *single-chain T-cell receptor* to a bacteriophage fusion protein. Instead, Onda merely reports fusing a part of the TCR (the V-α chain) to a bacteriophage coat protein.

Onda's fusion proteins are completely different from those described by the Applicants. For example, the V-α chain described by Onda is substantially smaller than the scTCR (includes V-α + V-β) which Applicants have successfully manipulated.

Further, Onda's smaller V-α chain fusions would be expected to have fewer problems than Applicants' larger scTCR fusion proteins.

More detailed disclosure relating to the structure of the single-chain TCR can be found in the Background section of Applicants' disclosure as well as Garboczi, D. et al. (1996) *Nature* 384: 134 and Garcia, K. C. (1996) *Science* 274: 209. As will be appreciated, the structure and function of the scTCR is strikingly different from the V-α chain taught by Onda.

Onada simply does not disclose fusion between a scTCR and a bacteriophage coat protein. Instead, Onda merely describes fusion with a small part of a TCR. The reference when taken by itself or in combination with the other cited references does not suggest, imply or provide any motivation to make the scTCR protein fusion as Applicants have done.

The position has also been taken that Onda teaches that a TCR-bacteriophage fusion protein can be used to study TCR interactions. Office Action at pages 7-8. The implication is that Onda's disclosure provides tools which can be used generally to analyze these interactions. However, Onda's molecules are reported to have very limited use. As an illustration, Onda reports that their Vα chain fusions have *unusual properties* that may not reflect typical TCR-ligand interactions:

> Our results extend these findings by demonstrating that the dominant interactions of certain TCRα chains for peptide antigens may be sufficiently high that they can be analysed independently. However, these interactions are ***quite unusual*** in that they do not require the expression of the second TCR subunit or normal MHC and coreceptor interactions. ***These results may raise concern that this model does not reflect typical TCR-ligand interactions***.
>
> Onda at page 1395, col. 1 (emphases added).

Additionally, only some of Onda's Vα chain fusion proteins are reported to function.

> ...only a subset of TCR Vα have capacity for direct interactions with antigen strong enough to be detectable in this system.
>
> Onda at page 1395, col. 2, second full paragraph.

Thus, one of skill having read Onda would not be taught or motivated to fuse a scTCR to a bacteriophage coat protein as Applicants have done. Indeed, it appears that many of Onda's V-α chain protein fusions do not work (ie. they do not bind antigen) and those that do are reported to be useful for studying "unusual" TCR-ligand interactions.

It is believed that Onda's disclosure when taken alone or in combination with the other cited references provides no suggestion, implication or motivation to make the presently claimed soluble fusion molecules. Additionally, Onda teaches away from the present invention by teaching that many V-α chain fusion proteins do not work. Accordingly, reconsideration of Onda as a prior art reference is requested.

The rejection has cited Schodin and Novotny as support for various scTCR molecules. The disclosed scTCRs are believed to owe their reported properties to highly specific conditions disclosed in the references.

For example, Schodin reports making an scTCR/thioredoxin fusion protein. However, there is no suggestion or motivation in Schodin taken by itself or in combination with the other cited references to substitute the thioredoxin with a bacteriophage coat protein as Applicants have done.

Novotny's scTCR is reported to bind FITC ligand after significant computer graphic and mutagenic manipulations. See the Office Action at page 9 and Novotny in the Abstract and page 8650. There is no teaching or suggestion in Novotny by itself or taken with the other cited references for taking the position that Novotny's already heavily manipulated scTCRs could be further changed to include a bacteriophage coat protein.

It is believed that the rejection oversimplifies the teachings of Schodin and Novotny by taking the position that these references teach scTCRs. Office Action at 10. At best, the references show how to solublize the scTCR by fusing to thioredoxin (Schodin) or mutating certain TCR genes to improve characteristics (Novotny).

Applicant respectfully disagrees with the Examiner's reading of Kappler. As understood, Kappler discloses methods of making a T-cell receptor (dimer) by using a vector carrying two separate αβ chains. Kappler's chains are reported to assemble as a heterodimer. See e.g., Kappler at page 8466, col. 1, first full paragraph. In contrast, the present invention shows how to make single chain fusion proteins (monomer) by using a vector carrying two fused αβ chains. Applicant's fusion protein is a single-chain rather than a heterodimer. Thus, the rejection's reliance on Kappler as a prior art reference is believed to be misplaced.

Applicant can find nothing in the Ward reference that remedies the above-mentioned defects in the cited art.

In view thereof, reconsideration and withdrawal of the §103 rejection is requested.

Claims 1-20 stand rejected under 35 U.S.C. §103 as being unpatentable over Barbas U.S. Patent 5,759,817 and Onda (*Molecular Immunol.* 32: 1387, 1995) in view of Schodin et al. (*Mol. Immunol.* 33: 819, 1996); Novotny et al. (*PNAS* 88: 8646, 1991), WO 96/18105, Ward (*Scand. J. Immunol.* 34: 215, 1991) or Kappler et al. (*PNAS* 91: 8462, 1994) and further in view of Choi et al. U.S. Patent 5,616,472).

For reasons discussed in the previous §103 rejection, Applicants respectfully disagree with the position that the Examiner's combination of Barbas and Onda taken with Schodin, Novotny, WO 96/18105, Ward or Kappler obviates Applicants' invention. The discussion under the previous §103 rejection is incorporated herein by reference in its entirety.

As understood, the Choi patent does not remedy the deficiencies discussed in the previous §103 rejection. Accordingly, reconsideration and withdrawal of the present §103 rejection is requested.